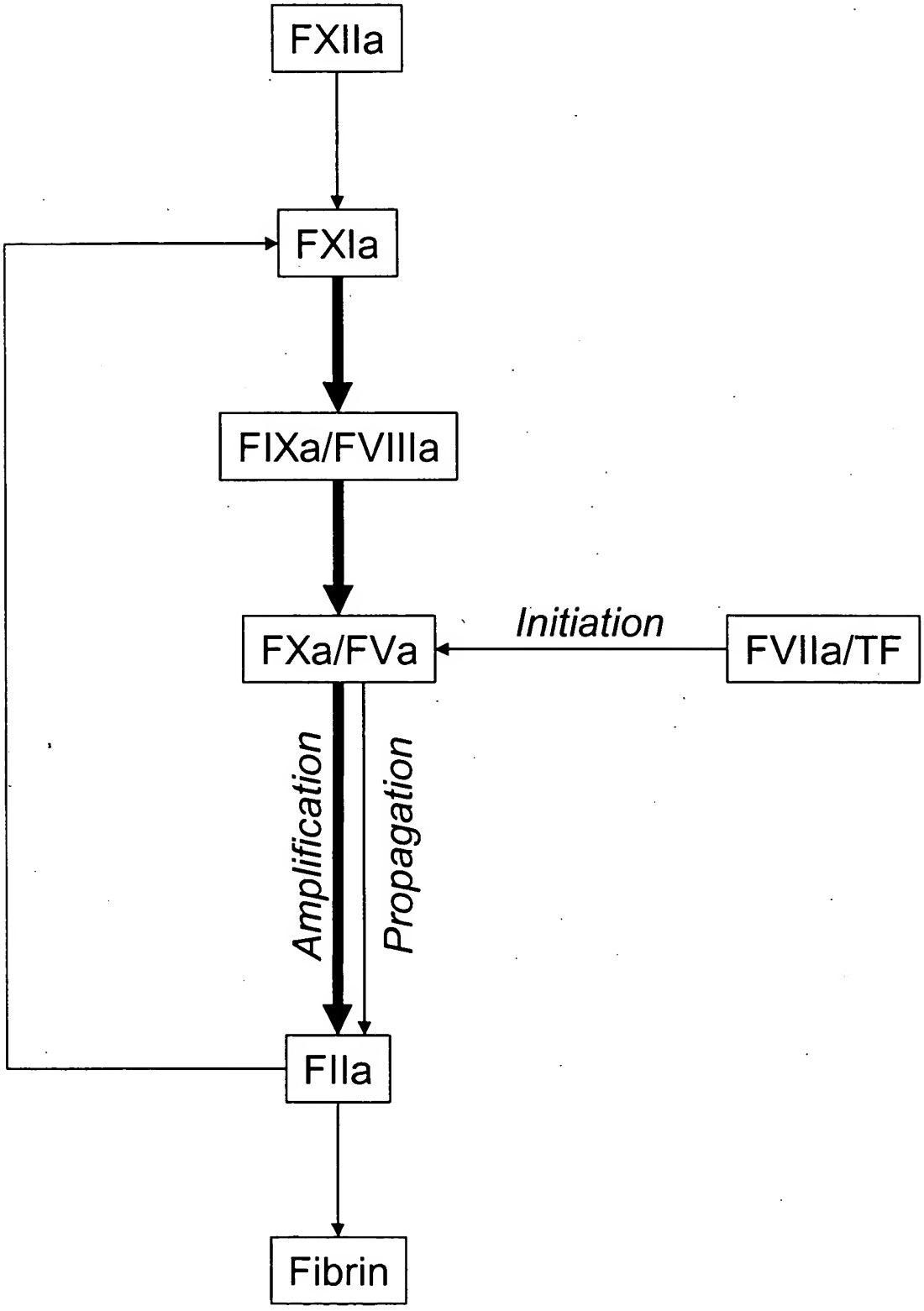

FXIIa
FXIa
FIXa/FVIIIa
FXa/FVa
Initiation
FVIIa/TF
Amplification
Propagation
FIIa
Fibrin

Figure 1

FXIcat	Residue	Trypsin	FXIcat	Residue	Trypsin	FXIcat	Residue	Trypsin
370	ILE	16	410	THR	54	450	ILE	90
371	VAL	17	411	ALA	55	451	HIS	91
372	GLY	18	412	ALA	56	452	ASP	92
373	GLY	19	413	HIS	57	453	GLN	93
374	THR	20	414	CYS	58	454	TYR	94
375	ALA	21	415	PHE	59	455	LYS	95
376	SER	22	416	TYR	5901	456	MET	96
377	VAL	23	417	GLY	5902	457	ALA	97
378	ARG	24	418	VAL	5903	458	GLU	98
379	GLY	25	419	GLU	60	459	SER	99
380	GLU	26	420	SER	61	460	GLY	100
381	TRP	27	421	PRO	62	461	TYR	101
382	PRO	28	422	LYS	63	462	ASP	102
383	TRP	29	423	ILE	64	463	ILE	103
384	GLN	30	424	LEU	65	464	ALA	104
385	VAL	31	425	ARG	66	465	LEU	105
386	THR	32	426	VAL	67	466	LEU	106
387	LEU	33	427	TYR	68	467	LYS	107
388	HIS	34	428	SER	69	468	LEU	108
389	THR	35	429	GLY	70	469	GLU	109
390	THR	36	430	ILE	71	470	THR	110
391	SER	37	431	LEU	72	471	THR	111
392	PRO	3701	432	ASN	73	472	VAL	112
393	THR	3702	433	GLN	74	473	ASN	113
394	GLN	3703	434	SER	75	474	TYR	114
395	ARG	3704	435	GLU	76	475	THR	115
396	HIS	38	436	ILE	77	476	ASP	116
397	LEU	39	437	LYS	78	477	SER	117
398	CYS	40	438	GLU	79	478	GLN	118
399	GLY	41	439	ASP	80	479	ARG	119
400	GLY	42	440	THR	81	480	PRO	121
401	SER	43	441	SER	8101	481	ILE	122
402	ILE	44	442	PHE	82	482	CYS	123
403	ILE	45	443	PHE	83	483	LEU	124
404	GLY	46	444	GLY	84	484	PRO	125
405	ASN	47	445	VAL	85	485	SER	126
406	GLN	48	446	GLN	86	486	LYS	127
407	TRP	51	447	GLU	87	487	GLY	128
408	ILE	52	448	ILE	88	488	GLU	129
409	LEU	53	449	ILE	89	489	ARG	130

Figure 2

490	ASN	131	530	ARG	171	570	HIS	204
491	VAL	132	531	TYR	172	571	LEU	209
492	ILE	13201	532	ARG	173	572	VAL	210
493	TYR	133	533	GLY	17301	573	GLY	211
494	THR	134	534	HIS	174	574	ILE	212
495	ASP	135	535	LYS	175	575	THR	213
496	CYS	136	536	ILE	176	576	SER	214
497	TRP	137	537	THR	177	577	TRP	215
498	VAL	138	538	HIS	178	578	GLY	216
499	THR	139	539	LYS	179	579	GLU	217
500	GLY	140	540	MET	180	580	GLY	218
501	TRP	141	541	ILE	181	581	CYS	219
502	GLY	142	542	CYS	182	582	ALA	220
503	TYR	143	543	ALA	183	583	GLN	221
504	ARG	144	544	GLY	184	584	ARG	222
505	LYS	145	545	TYR	18401	585	GLU	223
506	LEU	146	546	ARG	185	586	ARG	224
507	ARG	147	547	GLU	186	587	PRO	225
508	ASP	148	548	GLY	187	588	GLY	226
509	LYS	149	549	GLY	188	589	VAL	227
510	ILE	151	550	LYS	18801	590	TYR	228
511	GLN	152	551	ASP	189	591	THR	229
512	ASN	153	552	ALA	190	592	ASN	230
513	THR	154	553	CYS	191	593	VAL	231
514	LEU	155	554	LYS	192	594	VAL	232
515	GLN	156	555	GLY	193	595	GLU	233
516	LYS	157	556	ASP	194	596	TYR	234
517	ALA	158	557	SER	195	597	VAL	235
518	LYS	159	558	GLY	196	598	ASP	236
519	ILE	160	559	GLY	197	599	TRP	237
520	PRO	161	560	PRO	198	600	ILE	238
521	LEU	162	561	LEU	19801	601	LEU	239
522	VAL	163	562	SER	19802	602	GLU	240
523	THR	164	563	CYS	201	603	LYS	241
524	ASN	165	564	LYS	202	604	THR	242
525	GLU	166	565	HIS	20201	605	GLN	243
526	GLU	167	566	ASN	20202	606	ALA	244
527	CYS	168	567	GLU	20203	607	VAL	
528	GLN	169	568	VAL	20204			
529	LYS	170	569	TRP	203			

Figure 2 (Continued)

COLUMNS	DATA TYPE	FIELD	DEFINITION
1 – 6	Record name	"ATOM"	
7 – 11	Integer	serial	Atom serial number.
13 – 16	Atom	name	Atom name.
17	Character	altLoc	Alternate location indicator.
18 -20	Residue name	resName	Residue name.
22	Character	chainID	Chain identifier.
23 – 26	Integer	resSeq	Residue sequence number.
27	AChar	iCode	Code for insertion of residues.
31 – 38	Real (8.3)	x	Orthogonal coordinates for X in Angstroms.
39 – 46	Real (8.3)	y	Orthogonal coordinates for Y in Angstroms.
47 – 54	Real (8.3)	z	Orthogonal coordinates for Z in Angstroms.
55 – 60	Real (6.2)	occupancy	Occupancy.
61 – 66	Real (6.2)	tempFactor	Temperature factor.
73 – 76	LString(4)	segID	Segment identifier, left-justified.
77 - 78	LString(2)	element	Element symbol, right-justified.

Figure 3

FX1cat Residue Substitutions	Activity*	Crystal Type
WT	1.2	N.D.
S434A	N.D.	N.D.
T475A	N.D.	N.D.
S434A,T475A	N.D.	Needles, Solved w/Ecotin
S434A,T475A,K422A	N.D.	Needles
S434A,T475A,K437A	1.3	Needles, Cubic/ Solved w/benzamidine, Plates
S434A,T475A,K486A	N.D.	N.D.
S434A,T475A,K505A	1.1	Needles w/SPRL cmpds; Cubic/ Solved w/benzamidine
S434A,T475A,K509A	N.D.	Needles
S434A,T475A,C482S	N.D.	Needles
S434A,T475A,C482S,K437A	1.4	Needles & Cubic crystals, with benz. and SPRL cmpds
S434A,T475A,C482S,R479A	N.D.	Needles
S434A,T475A,C482S,K505A	N.D.	Needles and Cubic crystals
S434A,T475A,C482S,D476A	0.7	Needles and plates
S434A,T475A,AVC terminal truncation	N.D.	Needles
S434A,T475A,C482S,Y416S	N.D.	N.D.

*ratio of FXIcat mutant K_{cat}/native Factor XIa K_{cat}

Figure 4A

Inhibitor	Resolution	Space Group	Lattice Constants	Mutant*	Condition†
Ecotin M84R	2.2 Å	$P2_12_12_1$	a=44.6 Å, b=92.7 Å, c=186.9 Å, α=β=γ=90°	WT-degly	1
WT Ecotin	2.6 Å	$P2_12_12_1$	a=44.3 Å, b=91.9 Å, c=186.2 Å, α=β=γ=90°	WT-degly	1
Ecotin IX-D	3.0 Å	$P2_12_12_1$	a=45.4 Å, b=91.4 Å, c=188.6 Å, α=β=γ=90°	2m	2
Benzamidine	2.0 Å	I23	a=b=c=120.1 Å, α=β=γ=90°	3m-K455A	3
SPRL-122599	2.8 Å	I23	a=b=c=121.5 Å, α=β=γ=90°	3m-K455A	4
SPRL-121995	2.1 Å	I23	a=b=c=121.2 Å, α=β=γ=90°	3m-K455A	5
SPRL-124336	3.0 Å	$P3_2$	a=b=41.9 Å, c=103.8 Å, α=β=γ= 90°	3m-K455A	6
SPRL-123682	2.0 Å	I23	a=b=c=121.3 Å, α=β=γ=90°	3m-K455A	7
SPRL-123672	2.2 Å	I23	a=b=c=121.4 Å, α=β=γ=90°	3m-K455A	3
SPRL-123545	2.1 Å	I23	a=b=c=120.7 Å, α=β=γ=90°	3m-K455A	8
SPRL-122624	2.1 Å	I23	a=b=c=122.4 Å, α=β=γ=90°	3m-K455A	9
SPRL-123586	2.7 Å	$P2_1$	a=55.8 Å, b=70.3 Å, c=62.1 Å, α=γ= 90°, β=102.2°	3m-K455A	10

*WT-degly=wide type FXIcat that is chemically deglycosylated; 2m=FXIcat with mutations of S452A, T493A; 2m-K523A=FXIcat with mutations of S452A, T493A and K523A; 3m-K455A=FXIcat with mutations of S452A, T493A, C500S and K455A.

†Crystallization conditions:

1. 20% (w/v) PEG 1000, 0.1 M Na/K phosphate, pH 6.2.
2. 22% (w/v) PEGMME 2000, 0.1 M $(NH_4)_2SO_4$, 0.1 M Na cacodylate, pH 6.2
3. 2.0 M ammonium sulfate, 0.1 M Tris-HCl, pH 8.5.
4. 23% (w/v) PEG 4000, 0.2 M Li_2SO_4, 0.1 M Tris-HCl, pH 8.5.
5. 24% (w/v) PEG 4000, 0.16 M Li_2SO_4, 80 mM Tris-HCl, pH 8.5.
6. 30% (w/v) PEGMME 5000, 0.2 M $(NH_4)_2SO_4$, 0.1 M Tris-HCl, pH 7.6.
7. 18% (w/v) PEG 4000, 0.2 M Li_2SO_4, 0.1 M Tris-HCl, pH 8.5.
8. 30% (w/v) PEG 4000, 0.2 M Li_2SO_4, 0.1 M Tris-HCl, pH 8.5.
9. 20% (w/v) PEGMME 2000, 0.2 M $(NH_4)_2SO_4$, 0.1 M Tris-HCl, pH 7.6.
10. 1.4 M tri-sodium citrate, 0.1 M HEPES, pH 7.5.

Figure 4B

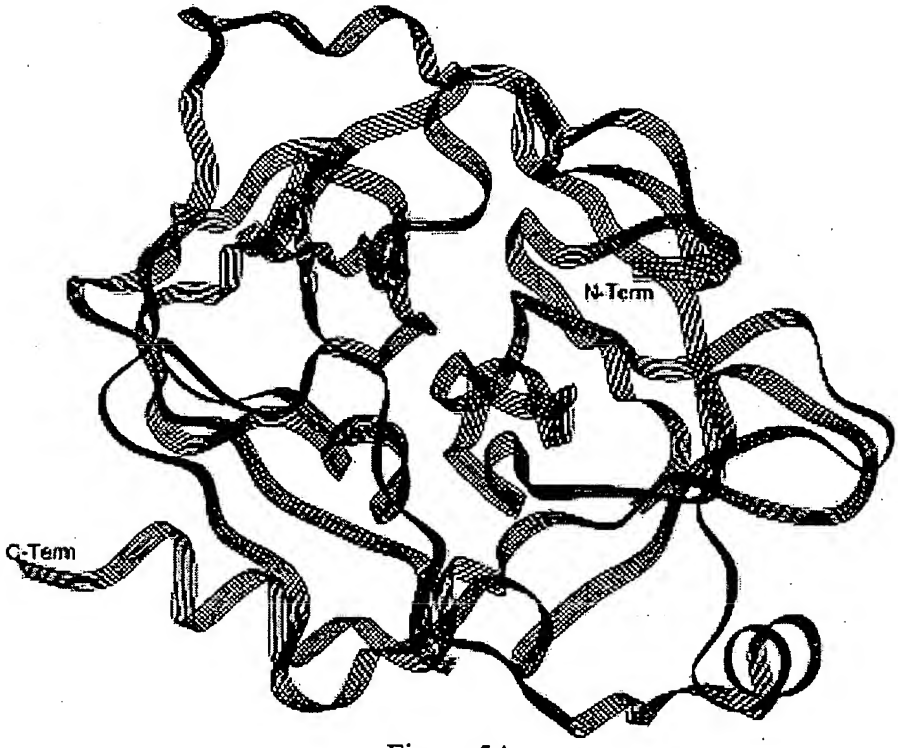


Figure 5A

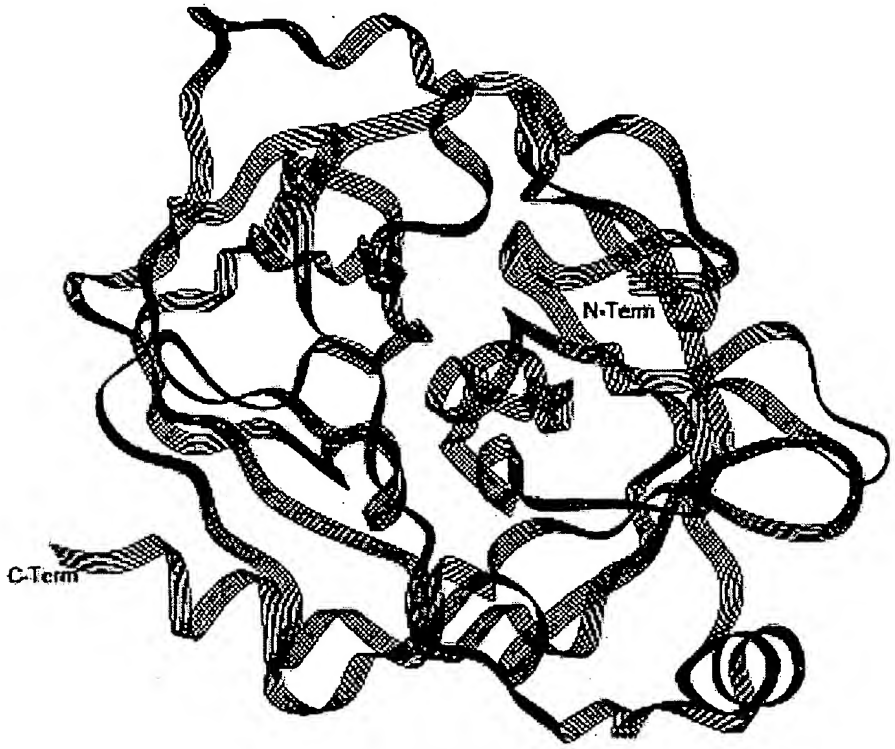


Figure 5B

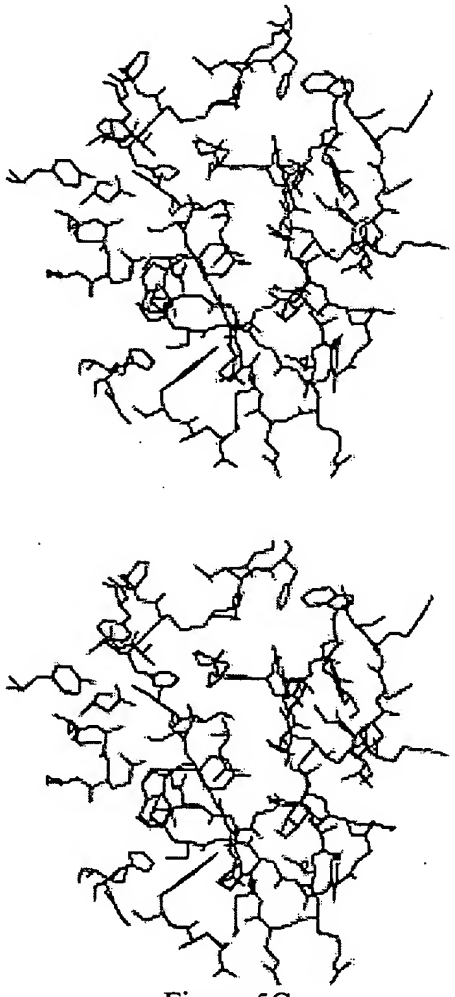


Figure 5C

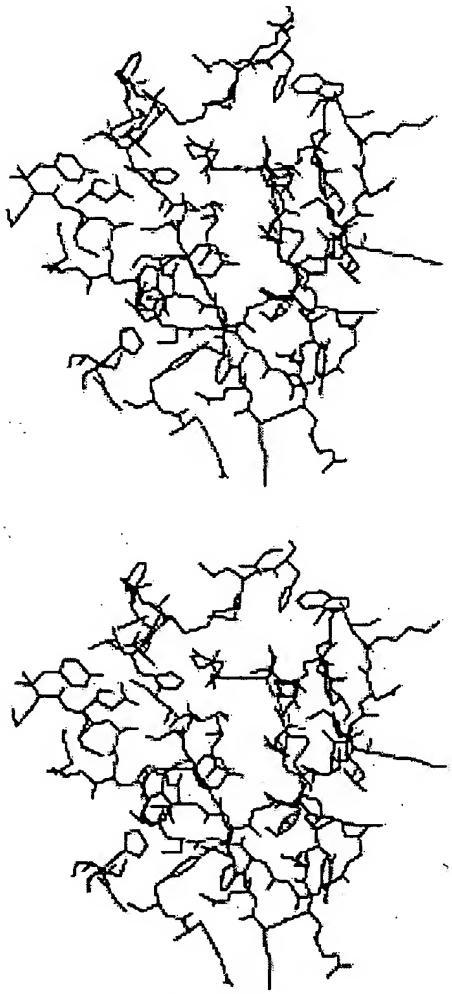


Figure 5D

Rat FXlcat sequence

GTGTTCGGAGGAGCTGCGTCTGTTCACGGCGAGTGGCCATGGCAGGTGACCCTGCA
CACCACCCAGGGACACCTGTGTGGAGGCTCCATCATTGGAAACCGGTGGATATTGA
CAGCGGCTCATTGTTTCTCTGGGACAGAGACACCTAAAACTCTGCGTGTCTACGGTG
GTATTGTAAATCAATCAGAAATAAATGAAGATACCACTTTCTTCAGGGTTCAAGAAA
TGATAATTCATGATCAATATACATCGGCAGAAAGTGGGTTTGACATTGCCCTCTTAA
AACTGGAACCGGCCATGAATTACACAGATTTTCAGCGGCCAATATGCCTGCCTTCCA
AAGGAGACAGAAACGTAGTTCACACAGAATGCTGGGTGACTGGATGGGGATACACA
AAATCAAGAGATGAAGTACAAAGTACTCTCCAGAAAGCCAAGGTACCATTGGTGTC
GAATGAAGAATGTCAAACAAGATACAGAAAACATAAAATAACCAACAAGGTGATCT
GTGCAGGATATAAGGAAGGAGGGAAGGATACGTGTAAGGGAGATTCTGGAGGGCC
CCTGTCCTGCAAACACAATGGGGTCTGGCACTTGGTGGGCATCACAAGCTGGGGTG
AAGGCTGCGGCCAGAAAGAGAGGCCGGGTGTCTACACCAACGTGGCCAAGTATGTG
GACTGGATTTTGGAGAAAACTCAGTCGGAATGA

Oligonucleotide positions used for cloning are indicated by the boxes

Figure 6

```
IVGGTASVRGEWPWQVTLHTTSPTQRHLCGGSIIGNQWILTAAHCFYGVE Human

VVGGAASVHGEWPWQVTLHIS---QGHLCGGSIIGNQWILTAAHCFSGIE Mouse
IVGGSASLPGEWPWQVTLHTVSPTQRHLCGGSIIGNQWILTAAHCFYGIE Rabbit
VFGGAASVHGEWPWQVTLHTT---QGHLCGGSIIGNRWILTAAHCFSGTE Rat

SPKILRVYSGILNQSEIKEDTSFFGVQEIIIHDQYKMAESGYDIALLKLE Human
TPKKLRVYGGIVNQSEINEGTAFFRVQEMIIHDQYTTAESGYDIALLKLE Mouse
SPKILRVYGGILNQSEIKEDTAFFGVQEIIIHDQYKTAESGYDIALLKLE Rabbit
TPKTLRVYGGIVNQSEINEDTTFFRVQEMIIHDQYTSAESGFDIALLKLE Rat

TTVNYTDSQRPICLPSKGDRNVIYTDCWVTGWGYRKLRDKIQNTLQKAKI Human
SAMNYTDFQRPICLPSKGDRNAVHTECWVTGWGYTALRGEVQSTLQKAKV Mouse
TTMNYTDSQRPICLPSKGDRNVIYTDCWVTGWGYRKLRDKIQNTLQKAKI Rabbit
PAMNYTDFQRPICLPSKGDRNVVHTECWVTGWGYTKSRDEVQSTLQKAKV Rat

PLVTNEECQKRYRGHKITHKMICAGYREGGKDACKGDSGGPLSCKHNEVW Human
PLVSNEECQTRYRRHKITNKMICAGYKEGGKDTCKGDSGGPLSCKYNGVW Mouse
PLLSNEECQKRYQRHEITSGMICAGYKEGGKDACKGDSGGPLSCKHNEVW Rabbit
PLVSNEECQTRYRKHKITNKVICAGYKEGGKDTCKGDSGGPLSCKHNGVW Rat

HLVGITSWGEGCAQRERPGVYTNVVEYVDWILEKTQAV              Human
HLVGITSWGEGCGQKERPGVYTNVAKYVDWILEKTQTV              Mouse
HLVGITSWGEGCAQRERPGIYTNVVKYLDWILEKTQAP              Rabbit
HLVGITSWGEGCGQKERPGVYTNVAKYVDWILEKTQSE              Rat
```

Figure 7

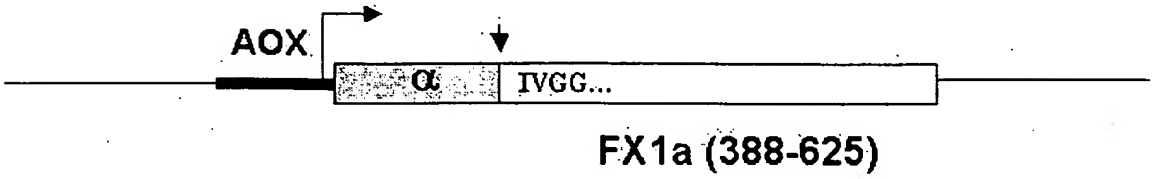


Figure 8

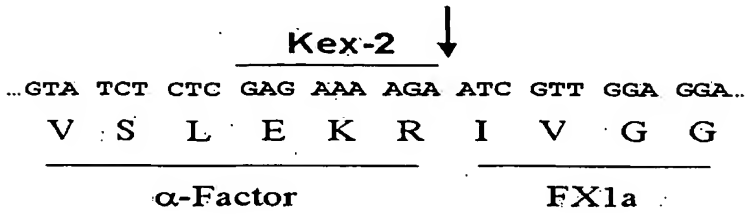
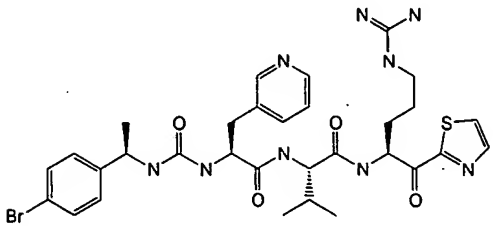

Kex-2
...GTA TCT CTC GAG AAA AGA ATC GTT GGA GGA...
V S L E K R I V G G
α-Factor
FX1a

Figure 9



SPRL-123529

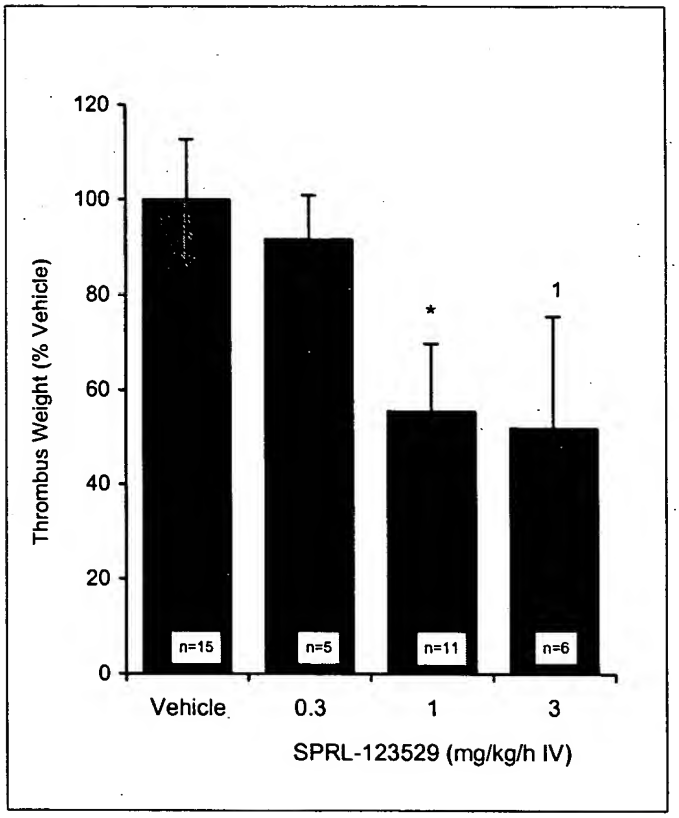


Figure 10

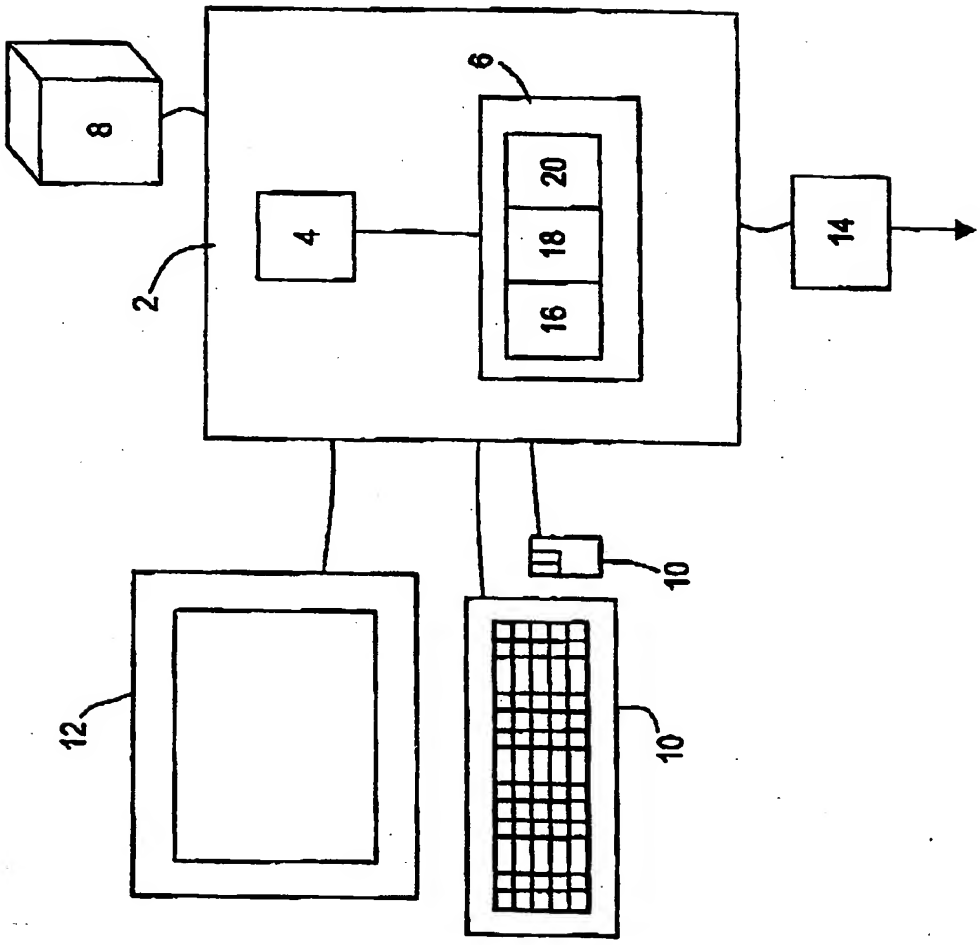


Figure 11

	M84R	wild type	IX-D	benz	122599	121995	124336	123682	123672	123545	122624
rms/loop	2.88/48	2.66/48	2.85/48	2.96/48	3.05/48	3.02/48	3.27/48	2.99/48	3.18/48	2.78/48	3.13/48
rms/fit	0.97/944	1.12/936	0.94/944	0.89/944	0.89/944	0.87/944	0.96/928	0.86/944	0.54/912	0.84/944	0.89/944
rms/loop	2.96/48	2.75/48	2.94/48	3.05/48	3.13/48	3.10/48	3.39/48	3.06/48	3.18/48	2.84/48	3.22/48
rms/fit	0.75/920	0.98/916	0.70/916	0.55/908	0.51/908	0.48/908	0.59/896	0.47/908	0.54/912	0.51/908	0.48/908

Figure 12

	M84R	wild type	IX-D	benz	122599	121995	124336	123682	123672	123545	122624
M84R		0.53	0.84	0.66	0.66	0.65	0.63	0.64	0.68	0.65	0.66
wild type	2952		0.95	0.80	0.88	0.86	0.58	0.86	0.89	0.81	0.91
IX-D	2948	2928		0.70	0.69	0.68	0.64	0.67	0.72	0.70	0.68
benz	932	924	928		0.29	0.27	0.65	0.28	0.33	0.28	0.31
122599	936	928	936	948		0.17	0.55	0.19	0.19	0.33	0.27
121995	940	924	940	948	948		0.49	0.11	0.22	0.30	0.23
124336	928	920	924	932	932	928		0.50	0.52	0.65	0.48
123682	940	924	940	948	948	948	928		0.21	0.27	0.22
123672	940	924	944	948	948	948	932	948		0.35	0.26
123545	940	928	936	948	948	948	932	948	948		0.37
122624	936	924	936	948	948	948	928	948	948	948	

Figure 13

	M84R	wild type	IX-D	benz	122599	121995	124336	123682	123672	123545	122624
M84R		0.54	0.88	0.77	0.76	0.73	0.66	0.71	0.74	0.71	0.75
wild type	2964		0.99	0.86	0.92	0.92	0.89	0.92	0.89	0.85	0.97
IX-D	2968	2948		0.82	0.77	0.74	0.70	0.73	0.87	0.76	0.75
benz	948	936	948		0.29	0.27	0.65	0.28	0.33	0.28	0.31
122599	948	936	948	948		0.17	0.55	0.19	0.19	0.33	0.27
121995	948	936	948	948	948		0.51	0.11	0.22	0.30	0.23
124336	932	924	932	932	932	932		0.52	0.52	0.65	0.50
123682	948	936	948	948	948	948	932		0.21	0.27	0.22
123672	948	924	952	948	948	948	932	948		0.35	0.26
123545	948	936	948	948	948	948	932	948	948		0.37
122624	948	936	948	948	948	948	932	948	948	948	

Figure 14

	M84R	wild type	IX-D	benz	122599	121995	124336	123682	123672	123545	122624
M84R		0.22	0.37	0.31	0.28	0.32	0.43	0.31	0.31	0.32	0.39
wild type	0.21		0.32	0.47	0.43	0.45	0.33	0.46	0.45	0.45	0.55
IX-D	0.45	0.32		0.28	0.32	0.34	0.36	0.31	0.34	0.28	0.39
benz	0.26	0.42	0.40		0.19	0.20	0.29	0.17	0.21	0.16	0.20
122599	0.25	0.38	0.29	0.20		0.04	0.23	0.08	0.06	0.23	0.17
121995	0.28	0.41	0.30	0.20	0.04		0.22	0.08	0.07	0.25	0.17
124336	0.42	0.34	0.36	0.30	0.24	0.22		0.22	0.20	0.35	0.23
123682	0.27	0.42	0.28	0.17	0.08	0.08	0.23		0.11	0.20	0.13
123672	0.28	0.45	0.31	0.21	0.06	0.07	0.21	0.11		0.26	0.17
123545	0.28	0.42	0.26	0.16	0.24	0.25	0.34	0.21	0.26		0.23
122624	0.35	0.50	0.34	0.20	0.22	0.17	0.24	0.13	0.17	0.22	

Figure 15

ATOMIC COORDINATE LISTINGS

(Incorporated by Reference as Table of Figure 16 Listings)

Figure 16